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PATENT & TRADEMARK OFFICE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Scott Miller

Examiner: KUMAR, Shailendra

Serial No.: 09/776,936

Group Art Unit: 1621

Filed: 12/22/98

Title: INHIBITION OF RAF KINASE USING SYMMETRICAL AND UNSYMMETRICAL SUBSTITUTED DIPHENYL UREAS

APPEAL BRIEF

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on August 3, 2005, please consider the following.

The attached check includes the fee as set forth under § 41.20(b)(2). The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is Bayer Corporation.

(ii) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(iii) STATUS OF CLAIMS

Claims 1 and 3-34 are pending in the present application.

Claims 12 and 14 are allowed.

Claims 1, 3-11, 13 and 15-34 were rejected. All rejected claims are on appeal.

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(iv) STATUS OF AMENDMENTS

No amendments were filed after final.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention is directed to compounds according to formula I, which are aryl urea compounds which inhibit the raf pathway (see page 2, lines 5-30), and also to methods of using compounds of formula II and IIa, which are aryl urea compounds, for the treatment of cancerous cell growth mediated by raf kinase (see page 4, last two lines on page to page 5, line 1 and page 7, lines 12-14), including the treatment of solid cancers, such as, for example, carcinomas, e.g., of the lungs, pancreas, thyroid, bladder or colon, and myeloid disorders, e.g., myeloid leukemia (see page 2, lines 14-17).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejections are:

(1) the rejections under 35 U.S.C. § 112, first paragraph, i.e., whether claims 15-19 and 28-33, directed to methods for the treatment of a cancerous cell growth mediated by raf kinase (including specific carcinomas named in claims 28-33) by compounds of formulae II and IIa, are enabled, and

(2) the rejections under 35 U.S.C. § 103, i.e., whether claims 1, 3-11, 13 and 20-34, directed to compounds of formula I, are unpatentable over Widdowson WO 96/25157, which reference does not teach or suggest the compounds of the present invention.

(vii) ARGUMENT

The Rejections Under 35 USC § 112

The Final Rejection dated May 3, 2005, rejects the method claims alleging that they are not enabled.

In a proper enablement rejection, which is not made here, first and foremost, a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling

support." (Emphasis added.) *In re Marzocchi*, supra. "The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra.* The Examiner has not provided support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is the subject of the method claims, which is enabled by the specification. The rejection therefore is improper under *In re Marzocchi.*

Instead, the Final Rejection alleges that applicants' arguments regarding the objectively doubtable standard "may be true for research purposes only. But this is not true for the actual treatment." See page 2, lines 7-8 from the bottom of the page. This is clearly contrary to the standards for enablement. There is nothing in the law of enablement regarding objective enablement for research purposes only, but not for actual treatment. Instead the Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), expressly stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

As can be seen, the discussion in *Brana* is directly relevant to the present case, where the art relates to the treatment of cancer and applicants provided adequate disclosure to objectively enable the claimed invention.

Applicants also point to *Bundy*, supra, where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity."

Additionally, the "purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles." See *In re Brana*, supra. Furthermore, there is no indication that one of ordinary skill in the art would have questioned the effect of the drugs in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005). Applicants here provided detailed disclosure of how to use the claimed compounds and also provided data in the form of examples demonstrating activity of the claimed compounds, which data is discussed later.

The Final Rejection also alleges that the rejections are "for the same reasons as set forth in the office action of 11/2/04, " where it was acknowledged that the specification points to various prior art literature publications on how to treat solid tumors and on the correlation of in vivo and in vitro inhibitory growth and the inhibition of ras kinase, but states that "the compounds of the claimed subject matter are vastly different than the cited prior art." Nothing in the prior art teaches or suggests, or even remotely supports a position that a new group of compounds different in structure than those already known to be useful for the claimed conditions, could not have such utility. As stated above, the first paragraph of section 112 requires nothing more than objective enablement. The Patent Office has provided no basis for doubting the objective truth of the asserted utility.

Applicants attached a copy of *Lemoine et al.*, "Overview of ras oncogenes and their clinical potential," Chapter 10, SciSearch 2000:751594, to the Reply filed February 2, 2005, in response to allegations that "there is no known anticancer agent, which is effective against cancer such as pancreatic, lung and colon, thyroid or bladder or that matter." *Lemoine et al.* teaches that pancreatic cancer, acute myeloid leukemia, colorectal cancer, thyroid cancer, and non-small-cell lung carcinoma are highly associated with the ras/raf kinase pathway, that bladder cancer, etc., are associated with the ras/raf kinase pathway to an intermediate extent, and that a variety of cancers are less associated with ras/raf. See table 10.2 on page 89 of the publication. Claims 28-33 herein are directed so methods of treatment of some of these disclosed diseases also identified by *Lemoine et al.* as related to the ras/raf kinase pathway. Also attached to that Reply were a copy of *Ravi et al.*, "Activated Raf-1 causes growth arrest in human small cell lung cancer cells," J. Clin. Invest., Vol. 10, No. 1, Jan. 1998, 153-159, for which the title speaks for itself. The Final Rejection dismisses this information by merely calling *Lemoine et al.* an "overview article," while alleging that "with respect to the patentability of the instant claimed method, there is no correlationship found in the instant

specification." Once again, it is respectfully submitted that based on what is known in the art and what is disclosed in the specification, there is no basis for doubting the objective truth of the asserted claimed utility; and thus, no basis for the rejections.

With respect to the "correlationship" allegation, applicants in the specification teach the compounds of the invention act on raf, teach how the activities of individual compounds can be determined, teach the activities of 144 exemplified compounds from the examples, and provide guidance as to administration modes and amounts throughout the specification. Applicants on page 74 of the specification teach in the biological examples section that in the in vitro raf kinase assay disclosed, all compounds exemplified, which are 144 compounds (see the tables), displayed IC_{50} values of between 1 nM and 10 μM, indicating to one of ordinary skill in the art that these compounds are effective in inhibiting raf kinase.

This data was also dismissed by the Final Rejection, which alleged that "it can be at most concluded that the instant claimed compounds can be used for treating chemokine mediated diseases." No evidence has been presented to support this restricted interpretation of this data.

Reversal of this rejection is respectfully requested for all the foregoing reasons.

The Rejection Under 35 USC § 103

The Final Rejection maintained the rejection of the compound claims over Widdowson despite there being no overlap in structure between the compounds of the reference and the current claims.

The groups -M-L^1 of the claimed compounds are not ortho-positioned on the phenyl ring neighboring the urea group as is the X_1R_2 group of Widdowson. All of the compounds claimed herein have hydrogen on both ortho-positions of the phenyl ring. Replacing the substituent "X_1R_2"of Widdowson with hydrogen would not be obvious in that Widdowson teaches that the "X_1R_2"substituent is required at this position.

Additionally, Widdowson requires that R_2 of the group X_1R_2 have a functional moiety that provides ionizable hydrogen having a pKa of 10 or less. The compounds of claims 1-11, 13, 14 and 20-26 do not require such an ionizable hydrogen (only claims 27 and 34 define compounds which do not require a pKa greater than 10). Thus, the compounds of claims 1-11, 13, 14 and 20-26 are structurally distinct from the compounds of Widdowson also based on this functional limitation. It would not be obvious to ignore the requirements

of Widdowson and prepare compounds with a pKa of greater than 10. Furthermore, there is neither evidence nor a hint or suggestion that positioning the group X_1R_2 at a position other than ortho will enable the functional moieties defined in the application to provide ionizable hydrogen having a pKa of 10 or less.

Claim 34 defines compounds where all M-L^1 groups are distinct in composition from the X_1R_2 groups of Widdowson, i.e., there is no hydroxyl group or other substituent with an ionizable hydrogen on the L^1 group. The compounds of claim 34 are not position isomers, for example, by even a very broad extrapolation from the compounds of Widdowson and are clearly unobvious in view of this reference.

Additionally, there are numerous dependent claims where there is no overlap, for example, claims 6 and 23, where the M groups are distinct from the corresponding X_1 group of Widdowson.

The substituents defined for L^1 in many claims herein do include the moiety "OH." As mentioned above, all claimed compounds where L^1 is substituted by OH are distinct from those of Widdowson since the hydroxy substituted group –M-L^1 is not at the ortho position of the phenyl ring. Even if the pKa requirements within claims 1-11, 12-14 and 20-26 are ignored and eliminated, as is the case for claim 27, the compounds defined are structurally unobvious. The compounds of claim 27 cannot be considered obvious position isomers of the reference's formula Ib since there is no direction or motivation to ignore the specific teachings of Widdowson with regard to the position of the group X_1R_1, i.e., to make all the right choices and selections which are necessary from the reference's generic formula Ib to arrive at a M-L^1 group consistent with this invention and place it at a meta- or para-position on the phenyl group.

The reference does not provide a single example of a compound of the reference's formula Ib. One of ordinary skill in the art is merely provided with a very generic formula Ib without any guidance as to what choices to make when making a compound of the reference. Additionally, not a single point of motivation is present in the reference for choosing R_2 to be substituted by OH versus other possibilities taught therein. Only a list of possible substituents is provided on page 21, lines 27-30, of the reference for R_2, of which one is hydroxy.

The Final Rejection on page 4 incorrectly alleges, while citing *In re Mehta*, 146 USPQ 284 (CCPA 1965) that "positions isomers are prima facie obvious as a whole, absent evidence to the contrary." There is no such *per se* rule, not even according to the case cited by the Examiner.

The CCPA set forth the test for obviousness for position isomers in *Mehta* stating that

> The fact that a position isomer of a compound is known is some evidence of the obviousness of that compound. Position isomerism is a fact of close *structural* similarity which is to be taken into consideration with all other relevant facts in applying the test of obviousness under 35 U.S.C. 103. It is the closeness of the relationship rather than the mere name, or, here, position number, which is significant, and which gives rise to an inference that the claimed compound is obvious.
>
> A compound is not, however, merely a structural formula; its properties as part of the whole must be considered. The similarity of *properties* of a reference compound as compared with a claimed compound gives rise to an even stronger inference of obviousness than that of structural similarity alone, and conversely, where the properties are different, they imply non-obviousness, when they are unexpected. (Internal citations omitted.)

In the *Mehta* case, obviousness was found since the "same moiety" substituted in a different position of a pyrrolidine ring was the only difference between the reference compounds and the claimed compounds and the properties of the reference compounds and the claimed compounds were also the "same." That is not the case here. Both the activity and uses of the compounds are different for the claimed compounds than the uses and activity of the reference compounds, i.e., the reference compounds are said to be useful for the treatment of chemokine mediated diseases, while the claimed compounds are useful for the treatment of a cancerous cell growth mediated by raf kinase. Nothing in the reference teaches or suggests that the compounds of the claims possess the claimed activity. Thus, under the test laid down by the court in *Mehta*, the different uses imply non-obviousness. Nothing in the case law provides support for the Office Action's position over the rejected claims.

Applicants point to *In re Dillon*, 16 USPQ2d 1897 (CAFC 1990), which provides a very extensive discussion of the caselaw on structural obviousness, including position isomers, and holds that "a *prima facie* case of obviousness of a new chemical compound or composition requires consideration of not only the chemical structure but also the newly discovered properties, in light of the teachings and suggestions of the prior art." Since in

Dillon there was "no objective teaching in the prior art that would have led one of ordinary skill to make [the claimed] product [therein] in order to solve the problem that was confronting Dillon," there was no finding of obviousness. Likewise here, there is no motivation in the reference to modify the compounds as alleged in solving the problem of treating the claimed cancers mediated by raf kinase.

Because nothing in the reference teaches or suggest compounds of the claims, the claims of the present application are not obvious.

Reversal of the rejection is respectfully requested.

Respectfully submitted,

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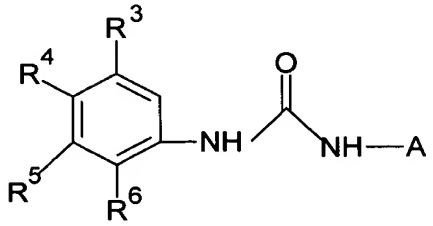
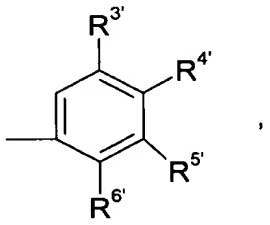
(viii) CLAIMS APPENDIX

1. A compound of formula I:



I

wherein A is



,

R^3, R^4, R^5 and R^6 are each, independently, H, halogen, NO_2,

C_{1-10}- alkyl, optionally substituted by halogen up to perhaloalkyl,

C_{1-10}-alkoxy, optionally substituted by halogen up to perhaloalkoxy,

C_{1-10}- alkanoyl, optionally substituted by halogen up to perhaloalkanoyl,

C_{6-12} aryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy, or

C_{5-12} hetaryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy,

and either

one of R^3, R^4, and R^5 is $-M-L^1$; or

two adjacent of R^3, R^4, R^5 and R^6 together are an aryl or hetaryl ring with 5-12 atoms, optionally substituted by C_{1-10}-alkyl, , halo-substituted C_{1-10}-alkyl up to perhaloalkyl, C_{1-10}-alkoxy, halo-substituted C_{1-10}-alkoxy up to perhaloalkoxy, C_{3-10}-cycloalkyl, C_{2-10}-

alkenyl, C_{1-10}-alkanoyl, C_{6-12}-aryl, C_{5-12}-hetaryl; C_{6-12}-aralkyl, C_{6-12}-alkaryl, halogen; NR^1R^1; -NO_2; -CF_3; -$COOR^1$; -$NHCOR^1$; -CN; -$CONR^1R^1$; -SO_2R^2; -SOR^2; -SR^2;

in which

R^1 is H or C_{1-10}-alkyl, optionally substituted by halogen up to perhaloalkyl and

R^2 is C_{1-10}-alkyl, optionally substituted by halogen, up to perhaloalkyl,

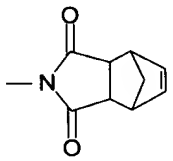
$R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$ are independently H, halogen,

C_1 - C_{10} alkyl, optionally substituted by halogen up to perhaloalkyl,

C_1 –C_{10} alkoxy optionally substituted by halogen up to perhaloalkoxy or two adjacent of $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$, together with the base phenyl, form a naphthyl group, optionally substituted by halogen up to perhalo, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkanoyl, C_{6-12} aryl, C_{5-12} hetaryl or C_{6-12} aralkyl;

M is –CH_2-, -S-, -$N(CH_3)$-, -NHC(O)- -CH_2-S-, -S-CH_2-, -C(O)-, or –O-; and

L^1 is phenyl, substituted by C_{1-10}-alkoxy, OH, -SCH_3, or by



pyridyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3, or NO_2,

naphthyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

pyridone, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

pyrazine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

pyrimidine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

benzodioxane, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

benzopyridine, optionally substituted by C_{1-10}-alkyl, one C_{1-10}-alkoxy, halogen, -OH, -SCH_3 or NO_2,

or

benzothiazole, optionally substituted by, C_{1-10} alkyl C_{1-10} alkoxy, halogen, OH, $-SCH_3$ or NO_2, and wherein the compound of formula I has a pKa greater than 10,

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein

R^3 is H, halogen or C_{1-10}- alkyl, optionally substituted by halogen, up to perhaloalkyl;

R^4 is H, halogen or NO_2;

R^5 is H, halogen or C_{1-10}- alkyl;

R^6 is H, C_{1-10}- alkoxy, thiophene, pyrole or methyl substituted pyrole,

$R^{3'}$ is H, halogen, C_{4-10}-alkyl, or CF_3 and

$R^{6'}$ is H, halogen, CH_3, CF_3 or $-OCH_3$.

4. A compound according to claim 1, wherein

$R^{3'}$ is C_{4-10}-alkyl, Cl, F or CF_3;

$R^{4'}$ is H, Cl or F ;

$R^{5'}$ is H, Cl, F or C_{4-10}-alkyl; and

$R^{6'}$ is H or OCH_3.

5. A compound according to claim 4, wherein $R^{3'}$ or $R^{5'}$ is t-butyl.

6. A compound according to claim 1, wherein M is $-CH_2-$, $-N(CH_3)-$ or $-NHC(O)-$.

7. A compound according to claim 6, wherein L^1 is phenyl or pyridyl.

8. A compound according to claim 1, wherein M is –O-.

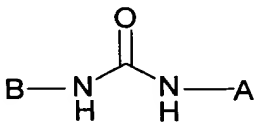
9. A compound according to claim 8, wherein L^1 is phenyl, pyridyl, pyridone or benzothiazole.

10. A compound according to claim 1, wherein M is –S-.

11. A compound according to claim 10, wherein L^1 is phenyl or pyridyl.

13. A pharmaceutical composition comprising a compound of claim 1, and a physiologically acceptable carrier.

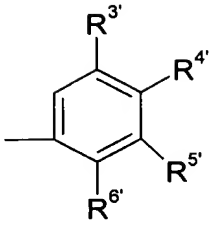
15. A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administering a compound of formula II:



II

or a pharmaceutically acceptable salt thereof wherein

A is



B is a substituted or unsubstituted, up to bicyclic aryl or heteroaryl moiety of up to 12 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n, wherein n is 0-3 and each W is independently selected from the group consisting of –CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl,C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, optionally substituted with halogen, C_1-C_{10} alkyl, or C_1-C_{10} alkoxy; C_7-C_{24} alkaryl, optionally substituted with halogen, C_1-C_{10} alkyl, or C_1-C_{10} alkoxy; C_3-C_{13} heteroaryl, optionally substituted with halogen, C_1-C_{10} alkyl, or C_1-C_{10} alkoxy; C_4-C_{23} alkheteroaryl, optionally substituted with halogen, C_1-C_{10} alkyl, or C_1-C_{10} alkoxy; substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_2-C_{10} alkenoyl, substituted C_1-C_{10} alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and $-M-L^1$;

wherein if W is a substituted group which does not contain aryl or hetaryl moieties, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, NO_2, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo;

wherein each R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} hetaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halo substituted C_2-C_{10} alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} hetaryl,

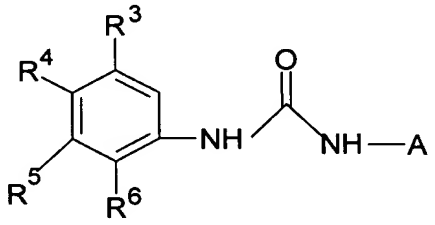
wherein M is - O-, -S-, $-N(R^7)-$, $-(CH_2)-_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-NR^7C(O)\ NR^7R^7-$, $-NR^7C(O)-$, $-C(O)NR^7-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a$, $-CX^a{}_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$,

m = 1-3, and X^a is halogen; and

L^1 is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur, which is unsubstituted or substituted by halogen up to per-halo and optionally substituted by Z_{n1}, wherein $_{n1}$ is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^7$, $-C(O)NR^7R^7$, -C(O)- NR^7, $-NO_2$, $-OR^7$, $-SR^7$, - NR^7R^7, $-NR^7C(O)OR^7$, $-C(O)R^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} hetaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein the one or more substituents of Z is selected from the group consisting of –CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$ and $-NR^7C(O)OR^7$,

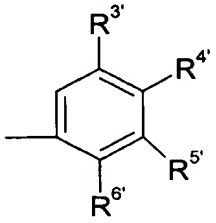
wherein $R^{3'}$, $R^{4'}$,$R^{5'}$and $R^{6'}$ are each independently H, halogen, C_{1-10}-alkyl, optionally substituted by halogen up to perhaloalkyl, C_1 –C_{10} alkoxy, optionally substituted by halogen up to perhaloalkoxy or two adjacent of $R^{3'}$,$R^{4'}$, $R^{5'}$ and $R^{6'}$ together with the base phenyl, form a naphthyl group, optionally substituted by halogen up to perhalo, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkanoyl, C_{6-12} aryl, C_{5-12} hetaryl or C_{6-12} aralkyl.

16. A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administering a compound of formula IIa:



IIa

wherein A is



R^3, R^4, R^5 and R^6 are each independently H, halogen, NO_2,

C_{1-10}- alkyl, optionally substituted by halogen up to perhaloalkyl,

C_{1-10}-alkoxy, optionally substituted by halogen up to perhaloalkoxy,

C_{1-10}- alkanoyl, optionally substituted by halogen up to perhaloalkanoyl,

C_{6-12} aryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy, or

C_{5-12} hetaryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy,

and either

one of R^3, R^4, R^5 and R^6 is –M-L^1; or

two adjacent of R^3, R^4, R^5 and R^6 together are an aryl or hetaryl ring with 5-12 atoms, optionally substituted by C_{1-10}-alkyl, halo-substituted C_{1-10}-alkyl up to perhaloalkyl, C_{1-10}-alkoxy, halo-substituted C_{1-10}-alkoxy up to perhaloalkoxy, C_{3-10}-cycloalkyl, C_{2-10}-alkenyl, C_{1-10}-alkanoyl; C_{6-12}-aryl, C_{5-12}-hetaryl, C_{6-12}-alkaryl, halogen; -NR^1R^1; -NO_2; -CF_3;-$COOR^1$; -$NHCOR^1$; -CN; -$CONR^1R^1$; -SO_2R^2; -SOR^2; -SR^2;

in which

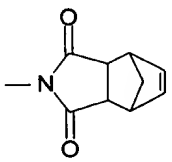
R^1 is H or C_{1-10}-alkyl, optionally substituted by halogen, up to perhalo and

R^2 is C_{1-10}-alkyl, optionally substituted by halogen,

$R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$ are independently H, halogen, C_1 - C_{10} alkyl, optionally substituted by halogen up to perhaloalkyl, C_1 –C_{10} alkoxy optionally substituted by halogen up to perhaloalkoxy or two adjacent of $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$, together with the base phenyl, form a naphthyl group optionally substituted by halogen up to perhalo, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkanoyl, C_{6-12} aryl, C_{5-12} hetaryl or C_{6-12} aralkyl, halogen up to perhalo;

M is –CH_2-, -S-, -$N(CH_3)$-, -NHC(O)- -CH_2-S-, -S-CH_2-, -C(O)-, or –O-; and

L^1 is phenyl, pyridyl, naphthyl, pyridone, pyrazine, pyrimidine, benzodiaxane, benzopyridine or benzothiazole, each optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3, NO_2 or, where Y is phenyl, by



or a pharmaceutically acceptable salt thereof.

17. A method according to claim 16, wherein

R^3 is halogen or C_{1-10}- alkyl, optionally substituted by halogen, up to perhaloalkyl;

R^4 is H, halogen or NO_2;

R^5 is H, halogen or C_{1-10}- alkyl;

R^6 is H , C_{1-10}- alkoxy, thiophene, pyrole or methylsubstituted pyrole

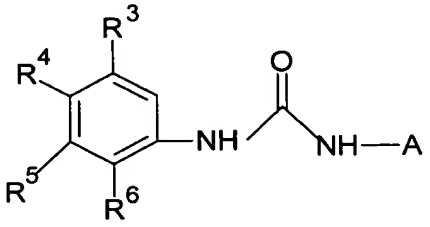
$R^{3'}$ is H, halogen, C_{4-10}-alkyl, or CF_3 and

$R^{6'}$ is H, halogen, CH_3 , CF_3 or OCH_3.

18. A method according to claim 16, wherein M is $-CH_2-$,–S-, $-N(CH_3)-$ or –NHC(O)- and L^1 is phenyl or pyridyl.

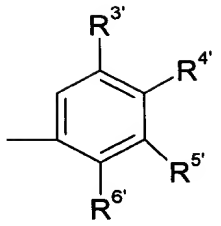
19. A method according to claim 16, wherein M is –O- and L^1 is phenyl, pyridone, pyrimidine, pyridyl or benzothiazole.

20. A compound of formula I:



I

wherein A is



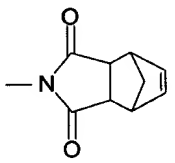
R^3, R^4 , R^5 and R^6 are each, independently, H, halogen, NO_2, C_{1-10}- alkyl, optionally substituted by halogen up to perhaloalkyl, C_{1-10}-alkoxy, optionally substituted by halogen up to perhaloalkoxy, pyridinyl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy, and one of R^3, R^4 , and R^5 is –M-L^1;

$R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$ are independently H, halogen, C_1 - C_{10} alkyl, optionally substituted by halogen up to perhaloalkyl, C_1 –C_{10} alkoxy optionally substituted by halogen up to perhaloalkoxy or two adjacent of $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$, together with the base phenyl, form a naphthyl group, optionally substituted by C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkanoyl, C_{6-12} aryl, C_{5-12} hetaryl or C_{6-12} aralkyl;

$R^{3'}$ is H, halogen, C_1 - C_{10} alkyl, optionally substituted by halogen up to perhaloalkyl, C_1 –C_{10} alkoxy optionally substituted by halogen up to perhaloalkoxy

M is –CH_2-, -S-, -$N(CH_3)$-, -NHC(O)- -CH_2-S-, -S-CH_2-, -C(O)-, or –O-; and

L^1 is phenyl, substituted by C_{1-10}-alkoxy, OH, -SCH_3, or by



pyridyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 , or NO_2,

naphthyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

pyridone, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

pyrazine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, -SCH_3 or NO_2,

pyrimidine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

benzodioxane, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

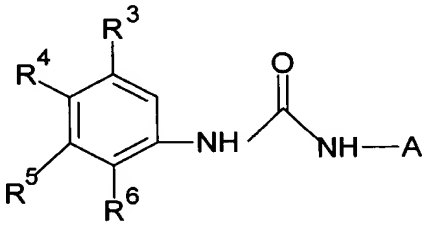
benzopyridine, optionally substituted by C_{1-10}-alkyl, OH, one C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2 ,

or

benzothiazole, optionally substituted by, C_{1-10} alkyl C_{1-10} alkoxy, halogen, OH, $-SCH_3$ or NO_2, and wherein the compound of formula I has a pKa greater than 10,

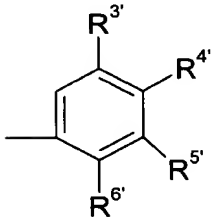
or a pharmaceutically acceptable salt thereof.

21. A compound of formula I:



I

wherein A is



,

wherein

R^3 is H, halogen or C_{1-10}- alkyl, optionally substituted by halogen, up to perhaloalkyl;

R^4 is H, halogen or NO_2;

R^5 is H, halogen or C_{1-10}- alkyl;

R^6 is H, C_{1-10}- alkoxy, thiophene, pyrole or methyl substituted pyrole,

$R^{3'}$ is H, Cl, F, C_{4-10}-alkyl, or CF_3 and

$R^{4'}$ is H, Cl or F ;

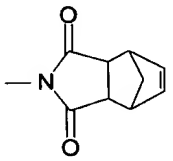
$R^{5'}$ is H, Cl, F or C_{4-10}-alkyl; and

$R^{6'}$ is H, halogen, CH_3, CF_3 or $-OCH_3$,.

and one of R^3, R^4 , and R^5 is $-M-L^1$; wherein

M is $-CH_2-$, -S-, $-N(CH_3)-$, -NHC(O)- $-CH_2-S-$, $-S-CH_2-$, -C(O)-, or –O-; and

L^1 is phenyl, substituted by C_{1-10}-alkoxy, OH, $-SCH_3$, or by



pyridyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$, or NO_2,

naphthyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyridone, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyrazine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyrimidine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

benzodioxane, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

benzopyridine, optionally substituted by C_{1-10}-alkyl, one C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2

,

or

benzothiazole, optionally substituted by, C_{1-10} alkyl C_{1-10} alkoxy, halogen, $-SCH_3$ or NO_2, and wherein the compound of formula I has a pKa greater than 10,

or a pharmaceutically acceptable salt thereof.

22. A compound according to claim 21, wherein $R^{3'}$ or $R^{5'}$ is t-butyl.

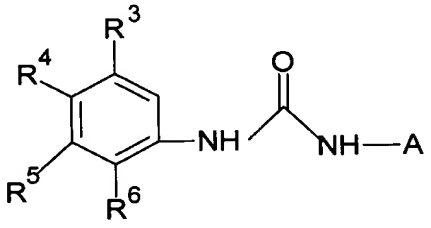
23. A compound according to claim 21, wherein M is $-CH_2-$, $-N(CH_3)-$ or $-NHC(O)-$.

24. A compound according to claim 21, wherein L^1 is phenyl or pyridyl.

25. A compound according to claim 21, wherein M is –S-.

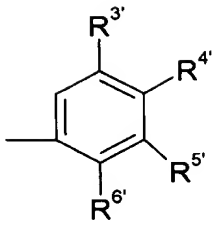
26. A compound according to claim 25, wherein L^1 is phenyl or pyridyl.

27. A compound of formula I:



I

wherein A is



R^3, R^4, R^5 and R^6 are each, independently, H, halogen, NO_2,

C_{1-10}- alkyl, optionally substituted by halogen up to perhaloalkyl,

C_{1-10}-alkoxy, optionally substituted by halogen up to perhaloalkoxy,

C_{1-10}- alkanoyl, optionally substituted by halogen up to perhaloalkanoyl,

C_{6-12} aryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy, or

C_{5-12} hetaryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy,

and either

one of R^3, R^4, and R^5 is –M-L^1; or

two adjacent of R^3, R^4, R^5 and R^6 together are an aryl or hetaryl ring with 5-12 atoms, optionally substituted by C_{1-10}-alkyl, , halo-substituted C_{1-10}-alkyl up to perhaloalkyl, C_{1-10}-alkoxy, halo-substituted C_{1-10}-alkoxy up to perhaloalkoxy, C_{3-10}-cycloalkyl, C_{2-10}-alkenyl, C_{1-10}-alkanoyl, C_{6-12}-aryl, C_{5-12}-hetaryl; C_{6-12}-aralkyl, C_{6-12}-alkaryl, halogen; NR^1R^1; -NO_2; -CF_3; -$COOR^1$; -$NHCOR^1$; -CN; -$CONR^1R^1$; -SO_2R^2; -SOR^2; -SR^2;

in which

R^1 is H or C_{1-10}-alkyl, optionally substituted by halogen up to perhaloalkyl and R^2 is C_{1-10}-alkyl, optionally substituted by halogen, up to perhaloalkyl,

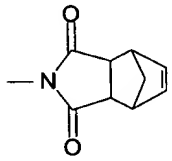
$R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$ are independently H, halogen,

C_1 - C_{10} alkyl, optionally substituted by halogen up to perhaloalkyl,

C_1 –C_{10} alkoxy optionally substituted by halogen up to perhaloalkoxy or two adjacent of $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$, together with the base phenyl, form a naphthyl group, optionally substituted by halogen up to perhalo, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkanoyl, C_{6-12} aryl, C_{5-12} hetaryl or C_{6-12} aralkyl;

M is $-CH_2-$, -S-, $-N(CH_3)-$, -NHC(O)- $-CH_2-S-$, $-S-CH_2-$, -C(O)-, or –O-; and

L^1 is phenyl, substituted by C_{1-10}-alkoxy, OH, $-SCH_3$, or by



pyridyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$, or NO_2,

naphthyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyridone, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyrazine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyrimidine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

benzodioxane, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

benzopyridine, optionally substituted by C_{1-10}-alkyl, one C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2 ,

or

benzothiazole, optionally substituted by, C_{1-10} alkyl C_{1-10} alkoxy, halogen, OH, $-SCH_3$ or NO_2, or a pharmaceutically acceptable salt thereof.

28. A method according to claim 16, wherein lung carcinoma is treated.

29. A method according to claim 16, wherein pancreas carcinoma is treated.

30. A method according to claim 16, wherein thyroid carcinoma is treated.

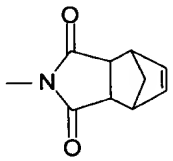
31. A method according to claim 16, wherein bladder carcinoma is treated.

32. A method according to claim 16, wherein colon carcinoma is treated.

33. A method according to claim 16, wherein myeloid leukemia is treated.

34 A compound according to claim 27, wherein

L^1 is phenyl, substituted by C_{1-10}-alkoxy, $-SCH_3$, or by



pyridyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, $-SCH_3$, or NO_2,

naphthyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2,

pyridone, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2,

pyrazine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2,

pyrimidine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2,

benzodioxane, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2,

benzopyridine, optionally substituted by C_{1-10}-alkyl, one C_{1-10}-alkoxy, halogen, $-SCH_3$ or NO_2

,

or

benzothiazole, optionally substituted by, C_{1-10} alkyl C_{1-10} alkoxy, halogen, $-SCH_3$ or NO_2.

(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None